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(54) Title: ARTIFICIAL BLOOD VESSEL

(57) Abstract

Artificial blood vessels having significantly improved anticlot characteristic and function, particularly for small-diameter artificial blood vessels. The artificial blood vessels, made of polyester, polyacrylonitrile or polyurethane, have their inner surfaces coated with 1 - 15 μm thick, preferably 3 - 10 μm thick, hydroxyapatite. The hydroxyapatite in the coating has a calcium atoms/phophorus atoms ratio either in the range of 1 - 1.5, preferably 1.3 - 1.4, or in the range of 1.75 - 2.5, preferably 1.8 - 2.2.

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Artificial Blood Vessel

Technical Field

The present invention pertains to artificial blood vessels, more specifically to artificial blood vessels which have significantly improved anti-clot characteristic and function well as small-diameter artificial blood vessels.

Background Art

Many patents on the artificial blood vessel have been applied and lively presentations and discussions have been continued at the conferences, etc. However, it is the artificial blood vessel of polyester fibers (Dacron) by DuPont woven in the tubular form and the artificial blood vessel of drawn out polytetrafluoroethylene that have been practically used in medical field.

These two share the market and use of other artificial blood vessels has been limited to exceptional circumstances or laboratory studies. Generally, for the large artificial vessels with diameters 8 - 36 mm, the use of the artificial blood vessel made of Dacron fabric is predominant, which has become a synonym for artificial blood vessel.

There are several methods of weaving fabrics used for artificial blood vessels, which are roughly divided into two types, namely, the plane weave and knit (meias). Blood leaks at the time of the transplantation and the seam must be closed with the blood itself or a fibrin glue. On the other hand, since pseudo intima is formed on the inner surface and it has a long-term advantage that it stabilizes with time. However, the formation of pseudo intima tends to decrease the inner radius and therefore it has not been widely used for small artificial blood vessels.

For the artificial blood vessel made of the drawn polytetrafluoroethylene, no initial blood leakage occurs, but it has a disadvantage that the pseudo intima does not develop on the inner surface as readily. Therefore, in the long run, it is inferior to the Dacron fabric artificial

blood vessel with respect to the biological compatibility including anti-clot characteristic. Nevertheless, it is often used for the artificial blood vessel with smaller diameters because the inner opening is more easily maintained because of the less pseudo intima.

Another unique example of artificial blood vessels was introduced in Science and Medical Applications of Hydroxyapatite, JAAS, 1991, pp. 185-189, TAKAYAMA Press System Center Co., Inc. However, this sintered hydroxyapatite is a brittle ceramic with extremely large elastic moduli and therefore its compliance is substantially different from that of actual blood vessel. Therefore it is valuable in laboratory study, but will not readily provide practical artificial blood vessels.

Disclosure of Invention

At present, for large artificial blood vessels with inner diameters greater than 8 mm, the artificial blood vessels available on the market pose no apparent difficulties. However, for small artificial blood vessels with 3 - 6 mm inner diameters, while many researches have been published, none of them have produced artificial blood vessels with satisfactory performance.

The primary reason for this is that there are the following two fundamental problems.

(a) Artificial blood vessels which have initially superior anti-clot characteristic at transplantation develop the pseudo intima slowly or does not develop it at all, thus the proportion of artificial blood vessels which remain open for a long period of time is small. On the other hand, artificial blood vessels which have poor initial anti-clot characteristic stabilize over a long period of time if the blockage does not ccur at the beginning. However, the blockage often occurs due to the initial blood clotting and consequently, the proportion of artificial blood vessels which remain open is also small.

(b) The blockage often occurs due to the thickening of the intima at anastosis, which develops several months after transplantation.

The inventor of the present invention, after concentrated efforts to resolve these difficulties, discovered that (1) Hydroxyapatite adsorbs a large amount of albumin among proteins in the blood plasma. lt is a common knowledge among researchers that the layer of albumin adsorption exhibits excellent anti-clot characteristic. (2) The less biologically compatible the artificial base material is, the more thickening of intima at anastomosis develops several months after transplantation.

On the basis of these discoveries, it is expected that hydroxyapatite which has proven excellent biological compatibility can be used for artificial blood vessels, and the use of hydroxyapatite for artificial blood vessels was introduced in the said literature. However, as previously described in the section of Existing Technology, when the artificial blood vessel is made of hydroxyapatite itself, such artificial blood vessel is not satisfactorily used in practice. The inventor therefore continued the research and developed the process of coating polymeric fabrics with hydroxyapatite, which lead to the present invention.

The methods for hydroxyapatite coating have been disclosed in many publications. Among them are: the sintering process in tokko Hei (1990) 13580; the plasma spray process for metallic implant materials in Tokko Sho 58 (1983) -50737; the plasma jet process for ceramic core materials in Tokko Sho 59 (1984) - 46911, Tokkai Sho 62 (1987) - 34539, Tokkai Sho 62 (1987) 57548, Tokkai Sho 63 (1988) - 46165 and others; the sputtering process in Tokkai Sho 58 (1983) - 109049; the flame jet process in the Proceedings of the Japan Ceramics Society 1988 1st Fall Symposium, reprint, pp. 401-402; the glass frit baking process in The Proceedings of the 9th Conference of Miomaterials Society (reprint, 1987, p. 6); the

electrophoresis process in The Japan Ceramics Society, 1988, pp. 417-418; and the processes to precipitate hydroxyapatit from an artificial body fluid composed of ions of the same type and concentration as those in human blood plasma in Tokko Sho 61 (1986) - 10939, Tokko Hei 1 (1989) - 54290 and Tokkai Hei 2 (1990) -255515.

As described above, various techniques for the hydroxyapatite coating have been published. Nevertheless, there remain many problems to be resolved, which include:
(a) The plasma jet process requires sophisticated and expensive equipment, and yet it does not readily produce fine coating and forms coating of apatite which is different from the apatite in the body because the source material, hydroxyapatite, is once melted at high temperatures.
(b) The sputtering process requires sophisticated and expensive equipment and forms coating of apatite which is different from the apatite in the body because hydroxyapatite, the source material, is once melted at high temperatures. (c) The sintering and glass frit processes require heat treatments at temperatures 850°C or above and therefore can be applied only to base materials with high heat resistance and may form coating of apatite which is different from the apatite in the body because hydroxyapatite, the source material, is once treated at high temperatures.
(d) The electrophoresis process can be applied only to metallic base materials with good electric conductivity because it uses the base material itself as an electrode and also forms coating of apatite which is different from the apatite in vivo because it uses sintered apatite as the source material.
(e) The process of pr cipitating hydroxyapatite from an artificial body fluid has a handicap that no base materials, other than CaO/SiO^2 base glass, which provide a good bonding with hydroxyapatite generated have been found.

As an example of the methods of (e) above, a process of coating polyester fabrics with hydroxyapatite has been published in Kinzoku (Metals), No. 12, 29-35 (1991). However, for hydroxyapatite having the calcium to phosphorus atomic ratio (Ca/P) close to its theoretical value 1.67, the bonding strength between such polyester fabric base material and the hydroxyapatite not sufficient and it is known that the bonding is easily separated under an external force and the corresponding strain. Therefore, it is obvious that it cannot be used for an artificial blood vessel in a living body where it is certainly subjected to repeated strains.

The present invention is intended to resolve the difficulties in the existing technology described above and to provide artificial blood vessels which have improved anti-clot characteristic and function well as small diameter artificial blood vessels.

ln order to achieve the objective described above, the inventor improved the method of (e) and successfully developed the artificial blood vessel pertaining to the present invention.

That is, the artificial blood vessel developed in the present invention has the following features.

(1) lt is composed of the base material of polymeric fabric coated with 1 15μm thick, preferably 3 - 10μm thick, hydroxyapatite.

(2) The range of Ca/P ratio of 'he said hydroxyapatite is 1.1 - 1.5, preferably 1.3 - 1.4.

(3) Or the range of Ca/P ratio of the said hydroxyapatite is 1.75 - 2.5, preferably 1.8 - 2.2.

(4) The said polymeric fabric is polyester, polyacrylonitrile or polyurethane, preferably polyester.

(5) A part of the phosphate or hydroxyl group in the said hydroxyapatite has been substituted by carbonic group.

The reasons for limiting the base material for the artificial blood vessel in this invention to polymeric fabrics are that their mechanical properties (such as the

compliance) required for the artificial blood vessel have already been optimized, that they have been well proven to be safely used in the body, and that it is considered sensible to coat the base material or polymeric fabric with hydroxyapatite in order to provide practicable artificial blood vessels.

The reasons for coating the base material with hydroxyapatite are that the said coating adsorbs albumin in the blood on contact and exhibits an excellent anti-clot characteristic, and that its excellent biological compatibility effectively reduces the thickening of intima at the anastomosis.

The reasons for limiting the range of thickness of hydroxyapatite coating in the artificial blood vessels pertaining to the present invention to 1 - 15 μm, preferably 3 - 10 μm, are that, if the thickness is below 1 μm, uniform coating is not reliably produced in practice and the hydroxyapatite may erode and disappear over a period of time after transplantation, and that, if the thickness exceeds 10 μm, its flexibility decreases significantly.

In addition, in the present invention, the range of the Ca/P ratio is limited to either 1.1 - 1.5, preferably 1.3 - 1.4, or 1.75 - 2.5, preferably 1.8 - 2.2. This is base on the following. If this ratio is below 1.1, the peak for hydroxyapatite crystal in the thin film X-ray diffraction almost disappears. If it ranges from 1.5 to 1.75, microcracks initiate in the coating formed, which readily lead to separation under cyclic strains encountered in practice. Also, if it exceeds 2.5, the peak for hydroxyapatite crystal in the thin film X-ray diffraction virtually disappears as well.

These behaviors may be reasoned as follows. The Ca/P ratio in hydroxyapatite is theoretically 1.67, whereas this ratio in actual living body is said to be about 1.5. The Ca/P ratio in the coating formed in the present invention deviated from the theoretical value promotes formation of

calcium phosphate in the microcrystalline or amorphous form in addition to hydroxyapatite, thus preventing crack initiation.

The presence of such microcracks greatly affects the bonding strength between polymeric fabric constituting the base material and hydroxyapatite, namely, significantly decreases the bonding strength and the flexibility.

ln addition, it was discovered that, when this ratio is shifted to a value greater than 1.67, that is that in the range of 1.7 - 2.5, the bonding strength between the polymeric fabric base material and hydroxyapatite coating formed, surprisingly, increases substantially. This fact had not been known at all previously.

In the present invention, the preferred polymeric fabrics used for the base material is polyester, polyacrylonitrile or polyurethane. Polyester is particularly preferred because the polyester base artificial blood vessel has been successfully used and is more reliable.

The preferable hydroxyapatite in the present invention is that with a part of its phosphate or hydroxyl group substituted by carbonic group, because in such form it is closer to hydroxyapatite in a living body and has better biological compatibility.

<u>Best Modes for Carrying Out the Invention</u>

The artificial blood vessel in the present invention is prepared as follows. The artificial blood vessel with inner diameter 6 mm made of polyester fabric USCI DeBakey P-005106 manufactured by Bird Co. is used for the base material and the glass powder, which has grain diameters 100 - 600μm and the composition presented in Tokkai Hei 2 (1990) -25515, is filled in the said artificial blood vessel.

The ranges of CAO and SiO^2 compositions in the said glass are

CaO .....20 - 60 mol%

SiO^2 ....40 – 80 mol%

and the composition of CaO and SiO^2 combined is at least 70 mol%. More than 80% of the glass powder has grain diameters 100 – 600μm.

The composition of the said glass is as follows.

CaO .....49.87 mol%

SiO^2..... 35.46

P^2O^5..... 7.153

MgO 7.111

CaF^2..... 0.399

The artificial blood vessel filled with the glass powder was immersed in an artificial body fluid A practically supersaturated with hydroxyapatite for 48 hours. The compositions of the artificial body fluids A and B are as follows.

	Artificial Body Fluid A	Artificial Body Fluid B
NaCl	7.996 g	11.994 g
$NaHCO^3$	0.350	0.525
KCl	0.224	0.336
$K^2HPO^4.3H^2O$	0.228	0.342
MgCl	0.305	0.458
$CaCl^2$	0.278	0.417
Na^2SO^4	0.071	0.107
1NHCl	approx. 45 ml	approx. 68 ml
Tris(hydroxymethyl) aminomethane	6.057	8.086

A carbonate $NaHCO^3$ is included in these artificial body fluids. It has been verified that the hydroxyapatite layer formed from such artificial body fluids has a part of its phosphate group or hydroxyl group substituted by carbonic group. Hydroxyapatite in a living body is also known to have carbonic group replacing a part of its phosphate group or hydroxyl group.

After the artificial blood vessel was immersed in the artificial body fluid for 48 hours, the glass powder was removed from the artificial blood vessel and the inside was cleaned. Then the artificial blood vessel was immersed in the artificial body fluid B for 1 week. This artificial blood vessel was removed from the artificial body fluid, rinsed with water and dried. Then it was sterilized by ethylene oxide gas in a sterilizing bag.

The thickness of hydroxyapatite coating was controlled by changing the duration of immersion in the artificial body fluid. Tables I and II summarize the results of the experiments described above for artificial blood vessels pertaining to the present invention, with various thicknesses of hydroxyapatite coating.

TABLE I

	Experiments						
	1	2	3	4	5	6	7
Thickness of Coating (μm)	--	0.8	1.5	3.8	9.2	15	18
Presence of Cracking	--	no cracks	no cracks	no cracks	no cracks	no cracks	no cracks
Ca/P Ratio	--	1.8	1.8	1.8	1.8	1.8	1.8
Flexibility	--	no problem	no problem	no problem	micro-cracks	cracks observed	partially separated
Anti-Clot Charact ristic after 1 month	moderate clotting observed	moderate clotting observed	a little clotting observed	no clotting			not tested
after 3 months	a little clotting observed	a little clotting observed	no clotting	no clotting			
after 6 months	no clotting	no clotting	no clotting	no clotting			
Thickening at Anasomosis after 3 months	moderate	moderate	minor	none			not tested
after 6 months	severe	severe	minor	none			

TABLE II

	Experiments						
	8	9	10	11	12	13	14
Thickness of Coating (μm)	10	10	10	10	10	9.5	10
Presence of Cracking	no cracks	no cracks	no cracks	no cracks	cracks observed	large cracks	no cracks
Ca/P Ratio	1.0	1.1	1.3	1.5	1.6	1.65	1.8
Flexibility	micro-cracks	micro-cracks	micro-cracks	micro-cracks	a little partially separated	a little partially separated	no problem
Anti-Clot Characteristic							
after 1 month	moderate clotting observed	a little clotting observed	no clotting	no clotting	trace of clotting	trace of clotting	no clotting
after 3 months	a little clotting observed	no clotting	no clotting	no clotting	trace of clotting	trace of clotting	no clotting
after 6 months	no clotting	no clotting	no clotting	no clotting	trace of clotting	trace of clotting	no clotting
Thick ning at Anasomosis							
after 3 months	minor	minor	none	none	none	none	none
after 6 months	severe	severe	minor	none	none	none	none

The Ca/P ratio in hydroxyapatite was controlled by adjusting the ratio of dipotassium hydrogenphosphate/calcium chloride and the hydrogen ion concentration in the artificial body fluid.

The observation of the thickness of hydroxyapatite coating and the cracking were made by a scanning electron microscope. The Ca/P ratio was measured by a polymer microanalyzer.

The tube fatigue tests were performed as follows. The artificial blood vessel coated with hydroxyapatite was fixed inside an elastomer tube with the inner diameter 7.6 mm and the length 150 mm and this tube was placed around a pulley so that it was subjected to repeated 90° bending. After fatigue loading by rotating the pulley at 200 r.p.m. for 30 minutes, the presence of separation and cracking of the coating was examined by a scanning electron microscope to evaluate the flexibility.

In addition, about 20 mm of pulmonary arteries of grown dogs were replaced by artificial blood vessels, which were removed and observed after 1 month, 2 months and 6 months to evaluate the anti-clot characteristic and thickening at anasomosis.

The features of the artificial blood vessel pertaining to the present invention described above made it possible to provide the artificial blood vessels which have much superior anti-clot characteristic and function well as a small-diameter artificial blood vessels.

Claims

1. An artificial blood vessel characterized in that said blood vessel includes a base material made of a polymeric fabric and a 1 - 15μm thick coating of hydroxyapatite.

2. The artificial blood vessel described in Claim 1 further characterized in that said coating of hydroxyapatite is 3 - 10μm thick.

3. The artificial blood vessel described in Claims 1 or 2 characterized in that the Ca/P ratio of said hydroxyapatite is in the range of 1.1 - 1.5

4. The artificial blood vessel described in Claims 1 or 2 characterized in that the Ca/P ratio of said hydroxyapatite is in the range of 1.3 - 1.4.

5. The artificial blood vessel described in Claims 1 or 2 characterized in that the Ca/P ratio of said hydroxyapatite is in the range of 1.75 - 2.5.

6. The artificial blood vessel described in Claims 1 or 2 characterized in that the Ca/P ratio of said hydroxyapatite is in the range of 1.8 - 2.2.

7. The artificial blood vessel described in Claims 1, 2, 3, 4, 5 or 6 characterized in that said polymeric fabric material is polyester, polyacrylonitrile or polyurethane.

8. The artificial blood vessel described in Claims 1, 2, 3, 4, 5, 6 or 7 characterized in that a part of a phosphate group or a hydroxyl group in said hydroxyapatite has been substituted by a carbonic group.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/04803

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61L27/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61L

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 389 713 (KYOTO UNIVERSITY) 3 October 1990 see page 6, line 41 - line 42 see page 7, line 24 ---	1
A	EP,A,0 437 975 (SUMITOMO) 24 July 1991 see column 4, line 43 - line 49; claims 4,7 ---	1,3-6
P,A	WO,A,9 307 916 (SHERWOOD MEDICAL) 29 April 1993 see page 9, line 1 - line 8; claims 1,2,12 ---	1

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
24 AUGUST 1993	06. 09. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	PELTRE CHR.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	DATABASE WPIL Week 8631, Derwent Publications Ltd., London, GB; AN 86-202289 & JP,A,61 135 670 (MITSUBISHI) see abstract -----	1

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9304803
SA 74471

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US-A- 5068122	26-11-91
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		US-A- 5128169	07-07-92
WO-A-9307916	29-04-93	JP-A- 5103827	27-04-93

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82